AN

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/365, 31/22, 31/19, 31/44, C07D 309/10, 309/30, 319/06, 213/64

A1

(11) International Publication Number: **WO 99/11258**

(43) International Publication Date: 11 March 1999 (11.03.99)

(21) International Application Number: PCT/EP98/05415

(22) International Filing Date: 26 August 1998 (26.08.98)

(30) Priority Data:

9718157.2	28 August 1997 (28.08.97)	GB
9806413.2	25 March 1998 (25.03.98)	GB

(71) Applicant *(for all designated States except AT US)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH–4058 Basel (CH).

(71) Applicant *(for AT only)*: NOVARTIS–ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A–1235 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BAUER, Wilfried [CH/CH]; Hohli Gasse 7, CH–4432 Lampenberg (CH). COTTENS, Sylvain [CH/CH]; Traubenweg 34, CH–4108 Witterswil (CH). GEYL, Dieter [DE/DE]; Weiherhofstrasse 16, D–79104 Freiburg (DE). WEITZ–SCHMIDT, Gabriele [DE/DE]; Steinbrecherstrasse 4, D–79189 Bad Krozingen (DE). KALLEN, Jörg [CH/CH]; Kaltbrunnenstrasse 41, CH–4054 Basel (CH). HOMMEL, Ulrich [DE/DE]; Vögisheimer Weg 9, D–79379 Müllheim (DE).

(74) Agent: BECKER, Konrad; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LYMPHOCYTE FUNCTION ANTIGEN–1 ANTAGONISTS

(57) Abstract

The present invention relates to compounds which bind to all or parts of the active binding "south pole pocket" of the LFA–1 I–domain and their uses as LFA–1 antagonists.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

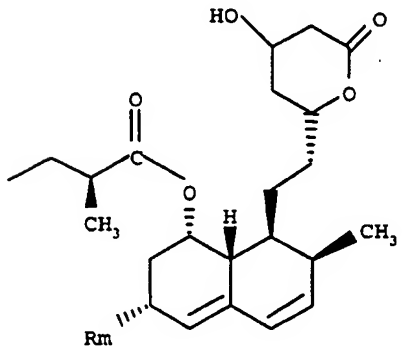
LYMPHOCYTE FUNCTION ANTIGEN-1 ANTAGONISTS

The present invention relates to compounds which bind to all or parts of the active binding "south pole pocket" of the LFA-1 I-domain and their uses as LFA-1 antagonists.

The lymphocyte function associated antigen LFA-1 belongs to the β2-integrins and plays an important role in T-cell activation and extravasation. Interactions of LFA-1 with its counter-receptors on endothelial and antigen presenting cells such as ICAM-1 or ICAM-3 are an important process in leucocyte endothelial cellular adhesion and migration which mediates disorders or diseases, e.g. autoimmune diseases, inflammation, ischemia/reperfusion injury and graft rejection after transplantation.

The so-called I-domain (Inserted Domain) of LFA-1 comprises a module of about 190 amino acids (Takada et al., Matrix Biology, 16, 143-151, 1997). The I-domain folds into a common structural motif comprising a central β-sheet surrounded by helices as determined by X-ray crystallography. (A. Qu & D. Leahy, Proc. Natl. Acad. Sci. USA, 92, 10277-10281, 1995).

Compactin and Mevinolin are fungal metabolites which have following formula:



R_m = H Compactin

R_m = CH_3 Mevinolin

They are disclosed e.g. by Y. Chapleur in "Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products", Springer Verlag, 1993, vol. 2, 829-937.

Mevinolin and most of the known analogues, e.g. pravastatin, mevastatin, simvastatin etc. have been found to be useful e.g. as 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG CoA R) inhibitors.

In accordance with the present invention, it has now surprisingly been found that mevinolin and derivatives thereof bind to LFA-1. Accordingly, the invention provides compounds for use in the treatment or prevention of autoimmune diseases, inflammation, ischemia/reperfusion injury and graft rejection which are preferably specific or substantially specific LFA-1 binding molecules, e.g. specific or substantially specific inhibitors of LFA-1/ICAM-1 or ICAM-3 interactions. Such compounds are preferably other than LFA-1 antibodies.

More particularly, it has been found that mevinolin binds to the LFA-1 I-domain between the C-terminal helix α7 and one side of the β-sheet (hereinafter the "south pole pocket"). X-ray analysis of the complex of LFA-1 I-domain with mevinolin shows that mevinolin does not bind to the MIDAS-site ("metal ion dependent adhesion site").

The complex, LFA-1 I-domain/mevinolin, is prepared by adding mevinolin (100mM solution in DMSO) to the protein solution (12.7mg/ml, 100mM $MgSO_4$), followed by crystallization. The structure is solved by molecular replacement (using the coordinates of apo LFA-1 I domain, A. Qu & D. Leahy, above) and has been refined to a R factor of 19.4% (R_{free} = 25.9%) using X-ray amplitudes in the resolution range 8Å-2.6 Å. The final model contains 2x 182 amino acids (amino acid residues 128 to 309 of the α-chain of LFA-1 which corresponds to the I-domain), 2 mevinolin molecules and a total of 86 water molecules.

Data collection statistics

	LFA-1 I-domain /Mevinolin
Temperature	293K

Wavelengh	1.5418Å
Resolution range	15.0Å-2.60Å
Spacegroup	$P2_12_12_1$
Unit cell dimensions	a=72.7Å, b=77.7Å, c=91.8Å
Measurements used	87179
Unique reflections	16457
Completeness	99.9% (99.8% in shell 2.69Å-2.60Å)
Multiplicity	5.3 (5.2)
Average I/sig(I)	13.9 (2.1)
Rmerge	11.6% (48.4%)

The south pole pocket is a cavity between one side of the central β-sheet (amino acids of β_1, β_3, β_4, β_5, preferably the side chains of such amino acids) and the α-helices α_1, α_7 (secondary structure of LFA-1 I-domain). Preferably the south pole pocket is the cavity defined by amino acids Val 130, Leu 132, Phe 134, Phe 153, Val 157, Leu 161, Tyr 166, Thr 231, Val 233, Ile 235, Ile 255, Tyr 257, Ile 259, Lys 287, Leu 298, Glu 301, Leu 302, Lys 305, particularly Leu 132, Phe 153, Val 157, Val 233, Ile 235, Tyr 257, Ile 259, Lys 287, Leu 298, Glu 301, Leu 302, Lys 305 of LFA-1 I-domain, more particularly by the side chains of such amino acids. In this pocket, the non-hydrogen atoms of mevinolin preferably interact within a distance of < 5Å, particularly 4-4.5Å.

The complex south pole pocket/mevinolin is energetically favored by hydrophobic, van der Waals and/or electrostatic interactions and possibly also by indirect hydrogen bonding.

As it will be appreciated, there are 2 complexes LFA-1 I-domain/mevinolin per asymmetric unit which are related by a non-crystallographic twofold axis. Figure 1 shows the monomeric part of the LFA-1 I-domain dimer as found in the asymmetric unit of the crystal together with the carboxy terminal region of the neighbouring monomer; the mevinolin ligand is shown as CPK-models. Figure 2 depicts the close-up of the south pole pocket of LFA-I domain with mevinolin.

As a result of its shape the south pole pocket as defined above favorably associates not only with mevinolin but with other chemical entities or ligands. Such entities or compounds are LFA-1 inhibitors or LFA-1/ICAM-1 or ICAM-3 interaction inhibitors.

The present invention provides any chemical entity or ligand, which binds in whole or in part to the south pole pocket of LFA-1 I-domain as defined above. Preferably the chemical entity or ligand interacts within a distance < 5Å, particularly 4-4.5Å. Suitable examples of such chemical entities include e.g. mevinolin derivatives. The elucidation of the mevinolin binding interactions on the LFA-1 I-domain south pole pocket provides the necessary information for designing new chemical entities and compounds that may interact in whole or part with the south pole pocket. Thus, the present invention permits the use of molecular design techniques e.g. computer modeling techniques, as a means of identifying, selecting and designing chemical entities or compounds capable of binding to the south pole pocket.

The design of compounds that bind to the south pole pocket according to the invention generally involves consideration of two factors. First, the entity must be capable of physically and structurally associating with parts or all of the south pole pocket. Non-covalent molecular interactions important in this association include hydrophobic, van der Waals interactions, hydrophobic interactions and/or electrostatic interactions and possibly also hydrogen bonding.

Second, the entity must be able to assume a conformation that allows it to associate with the south pole pocket directly. Although certain portions of the entity will not directly participate in these associations, those portions of the entity may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical entity in relation to all or a portion of the south pole pocket, or the spacing between functional groups of an entity comprising several chemical entities that directly interact with the south pole pocket.

The chemical entities which interact in whole or in part with the south pole pocket, preferably in a way similar to that of mevinolin may further be tested for their ability to inhibit LFA-

1/ICAM-1 or ICAM-3 interactions, using the Jurkat or Hut 78 cell assay described below under A). Representative compounds which bind to the south pole pocket according to the invention are those which inhibit the adhesion of Jurkat or Hut 78 cells to ICAM-1 with an $IC_{50} \leq 30\mu M$. These compounds are indicated as LFA-1 antagonists or LFA-1/ICAM-1 or ICAM-3 interaction inhibitors.

Preferred compounds of the invention for use in accordance with the invention are mevinolins (hereinafter referred to as "mevinolins of the invention"), preferably those having no or only limited HMG CoA R inhibitory activity.

Accordingly, the invention provides:

1. A compound for use in the treatment and/or prevention of autoimmune diseases, acute or chronic inflammatory diseases, ischemia/reperfusion injury, acute or chronic rejection of organ or tissue allo- or xenografts or infection diseases by virtue of its LFA-1 inhibitory activity.

   1.1 A compound for use in the treatment and/or prevention of autoimmune diseases, acute or chronic inflammatory diseases, ischemia/reperfusion injury, acute or chronic rejection of organ or tissue allo- or xenografts or infection diseases, the compound binding in whole or part to the south pole pocket, e.g. as defined above, e.g. with an interaction at a distance < 5Å, preferably 4-4.5Å.

   1.2 Mevinolins for use in the treatment and/or prevention of autoimmune diseases, acute or chronic inflammatory diseases, ischemia/reperfusion injury, acute or chronic rejection of organ or tissue allo- or xenografts or infection diseases, by virtue of their LFA-1 inhibitory activity.

   1.3 Mevinolins for use in the treatment and/or prevention of autoimmune diseases, acute or chronic inflammatory diseases, ischemia/reperfusion injury, acute or chronic rejection of organ or tissue allo- or xenografts or infection diseases,

which bind in whole or in part to the south pole pocket, e.g. as defined above, e.g. with an interaction at a distance < 5Å, preferably 4-4.5Å.

1.4 Mevinolins for use in the treatment and/or prevention of autoimmune diseases, acute or chronic inflammatory diseases, ischemia/reperfusion injury, acute or chronic rejection of organ or tissue allo- or xenografts or infection diseases, according to 1.2 or 1.3, which inhibit HMG CoA R activity with an $IC_{50} \geq 1\mu M$ in the InVitro Microsomal Assay of HMG CoA R Inhibition as disclosed below.

2. A method for producing a chemical entity or ligand which associates with the LFA-1 I-domain south pole pocket comprising the steps of:
   a. employing computational means to perform a fitting operation between the chemical entity and the south pole pocket; and
   b. analyzing the results of said fitting operation to quantify the association between the chemical entity and the south pole pocket.

In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition

200 µl aliquots (1.08-1.50 mg/ml) of rat liver microsomal suspensions, freshly prepared from male Spargue-Dawley rats (150-225 g body weight), in Buffer A with 10 mmol dithiothreitol are incubated with 10 µl test substance dissolved in dimethylacetamide and assayed for HMG CoA R activity as described by Ackerman et al., J Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG CoA R enzyme which catalyses the reduction of HMG CoA R to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HGM CoA R reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG CoA R is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate of test substances compared to controls and is expressed as IC_{50} (concentration of test substance which inhibits 50% of HMG CoA R activity).

The utility of the compounds of the invention, e.g. the mevinolins of the invention as inhibitors of LFA-1/ICAM-1 or ICAM-3 interactions may be demonstrated in following

test methods:

A. In vitro

Jurkat or Hut 78 cells obtained from ATCC and cultured in RPMI-1640 supplemented with 10% FCS, L-glutamine, non essential amino acids and 0.05mM 2-mercaptoethanol, are centrifuged, washed once in PBS, and resuspended at $0.5x10^6$ cells/ml in binding buffer (1.5% BSA, 5mM glucose, 2mM $MgCl_2$, 2ml $MnCl_2$ in TBS, pH 7) containing 5µg/ml BCECF-AM (Molecular Probes). The cells are incubated at 37°C for 30-45 min. in the dark. Then the cells are centrifuged and resuspended in binding buffer by pipetting and immediately used for experiment.

Flat well microtiter plates (NUNC Maxisorp) are coated with 1µg/ml goat anti-mouse Cκ (Bioreba, South.Biot.) in carbonate buffer (15mM Na_2CO_3, 35mM $NaHCO_3$, pH8.0) 2 hours at 37°C. The plates are emptied and blocked with 1.5% BSA and 0.5% Tween-20 in carbonate buffer for 90 min. at 37°C. The plates are emptied and washed once in TBS containing, 1.5% BSA. Baculovirus derived ICAM-1 mouse Cκ fusion protein (100ng/ml in TBS/1.5% BSA) is added to the wells. The plates are incubated for 90 min. at 37°C. After three washes with TBS/1.5%BSA, the compound to be tested is diluted in binding buffer (as above but free from BSA and glucose) and added to the wells. Then 100 000 Jurkat or Hut 78 cells/well are added and allowed to adhere for 30 min. at 37°C. Adherent cells are separated from non-adherent cells by 2-4 washes using binding buffer. Adherent cells are quantified with a fluorescence ELISA reader CytofluorII with the filters set at 485nm and 530nm emission.

In this assay, compounds of the invention inhibit adhesion of the Jurkat or Hut 78 cells to ICAM-1 with an $IC_{50} \leq 30$ µM, preferably 0.05 to 30 µM.

B. In vivo

i) Murine Thioglycollate Induced Peritonitis

Thioglycollate is injected i.p. to mice and immediately thereafter the compound to be tested is given s.c.. The mice are killed after 4 hours, the peritoneal cavity lavaged and the total number of neutrophils in the lavage fluid is determined.

In this assay, the compounds of the invention, e.g. mevinolins inhibit thioglycollate induced neutrophil migration when administered s.c. at a dose of from 0.001-50 mg/kg.

ii) Ischemia/Reperfusion Injury

The compounds may be tested in a model of heart ischemia/reperfusion injury (Abdeslam Oubenaissa et al., Circulation, 94, Suppl. II, 254-258, 1996) or as follows:

Mice weighing 20 - 25 g are anaesthetized with isoflurane and the right renal vessels are clamped using microvascular clamps for 60 min. After 60 min of ischemia, the microvascular clamps are removed. The left renal vessels (renal artery, vein and ureter) are ligated using a 4-0 surgical suture. The left (nonischemic) kidney is removed, and the abdominal cavity closed with 3-0 surgical suture. Sham groups undergo the same procedures as the ischemia group, but without clamping of the reight renal vessels.

Animals are sacrified by CO_2 inhalation at 24 h, 1 week and 2 weeks following reperfusion. Blood samples are collected by cardiac puncture into a 3.0 ml Vacutainer® tube (Becton-Dickensen) containing 0.04 ml of a 7.5% solutio of K_3 EDTA immediately after sacrifice. Plasma is separated and stored at -20°C until further analysis. Plasma creatinine and blood urea nitrogen (BUN) are analysed using Sigma procedures. Following sacrifice, the kidney is flushed with physiological saline, immediately snap-frozen in liquid nitrogen and stored at -70°C until analysis. Myeloperoxidase activity (MPO) in the kydney is measured according to the method of Bradley et al (J. Invest. Dermatol., 78, 206-209, 1982).

In this model, the compounds of the invention, e.g. the mevinolins reduce plasma creatinine and blood urea nitrogen when administered at a dose of 0.001 to 50 mg/kg, particularly for 4 days prior to ischemia.

iii) Vascularized heterotopic heart transplantation

Mice donor hearts are implanted onto the recipients abdominal vessels: brachiocephalic trunk to aorta and right pulmonary artery to inferior vena cava with end-to-side anastomoses using 11/0 Ethilon (Ethicon, Norderstedt, Germany) continuous sutures. Animals are closed in two layers with 6/0 Vicryl (Ethicon) and kept warm until fully recovered. Total ischaemia times are in the range of 40-50 min of which 25-35 min are at 4°C. During anastomosis (10-15 min) the graft is kept cold.

After transplantation, graft function is monitored by daily assessment of graft beat (palpation). Rejection is considered to be complete when heart beat stops. In all experiments rejection is confirmed by histological examination of the grafts. Significant improvements of graft function are obtained in animals treated with a compound of the invention, e.g. a mevinolin, administered at daily a dose ≤ 50 mg/kg.

The compounds of the invention, e.g. the mevinolins of the invention are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by LFA-1/ICAM-1 interactions e.g. ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, acute or chronic rejection of organ or tissue allo- or xenografts, acute or chronic inflammatory or autoimmune diseases, e.g. rheumatoid arthritis, asthma, allergy conditions, dermatological diseases, e.g. psoriasis, contact dermatitis, adult respiratory distress syndrome, inflammatory bowel disease and ophthalmic inflammatory diseases, infection diseases such as septic shock, traumatic shock.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, however, satisfactory results are achieved at dosage rates of from about 0.5 to 80 mg/kg animal body weight. Suitable daily dosage rates for larger mammals, for example humans, are of the order of from about 20 mg to 1.5 g/day, e.g. 100 mg to 1,5 g/day conveniently administered once, in divided dosages 2 ot 4 x / day, or in sustained release form. Unit dosage

forms suitably comprise from about 5 mg to 0.750 g of a compound of the invention, together with a pharmaceutical acceptable diluent or carrier therefor.

The mevinolins of the invention may be administered in free form or in pharmaceutically acceptable salt form e.g. acid addition salts or alkali salts such as sodium or potassium, or substituted or unsubstituted ammonium salts. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

3. A method for preventing or treating disorders or diseases mediated by LFA-1/ICAM-1 interactions, e.g. such as indicated above in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of the invention, e.g. a mevinolin of the invention or a pharmaceutically acceptable salt thereof;

4. A pharmaceutical composition for use in the method as in 3) above comprising a compound of the invention, e.g. a mevinolin in free form or pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

5. A compound of the invention, e.g. a mevinolin or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in the method as in 3) above.

The pharmaceutical compositions may be manufactured in conventional manner.

The compounds of the invention, e.g. the mevinolins of the invention may be administered by any conventional route, for example enterally, preferably orally, e.g. in the form of tablets or capsules or parenterally e.g. in form of injectable solutions or suspensions, or in a nasal or a suppository form.

The mevinolins of the invention may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens or other anti-inflammatory agents for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders. For example, they may be used in combination with cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; brequinar; FTY 720; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, or CD58 or their ligands; or other immunomodulatory compounds, e.g. CTLA4Ig, or other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including Selectin antagonists and VLA-4 antagonists.

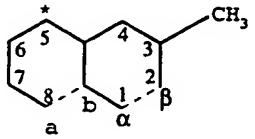
Where the mevinolins of the invention are administered in conjunction with other immunosuppressive / immunomodulatory or anti-inflammatory therapy, e.g. for preventing or treating chronic rejection as hereinabove specified, dosages of the co-administered immunosuppressant, immunomodulatory or anti-inflammatory compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a cyclosporin, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

6. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a mevinolin of the invention in free form or in pharmaceutically acceptable salt form, and a second drug substance, said second drug substance being an immunosuppressant, immunomodulatory or anti-inflammatory drug, e.g. as indicated above.

7. A kit or package for use in any method as defined under 3) above, comprising a mevinolin of the invention, in free form or in pharmaceutically acceptable salt form, with at least one pharmaceutical composition comprising an immunosuppressant,

immunomodulatory or anti-inflammatory drug. The kit or package may comprise instructions for its administration.

Representative mevinolins for use in accordance with the invention are those comprising a moiety of formula A

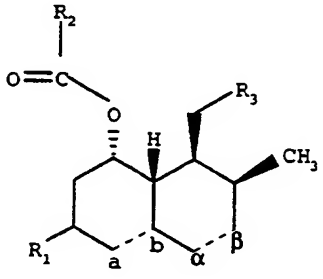


A

which is further substituted in positions 4 and 5 and optionally in positions 6 or 7, each of a---b and α---β, independently being a single or double bond. Each of a---b and α---β may also be part of a cyclopropyl group. The moiety of formula A may be substituted in positions 4, 5, 6 and/or 7 with one or more substituents as described in literature for known mevinolins, e.g. as disclosed by Y. Chapleur (see above). Preferably the substituent in position 4 is a substituted methyl group. Preferably the substituent in position 5 is linked via -*O-CO- to the bicyclic residue; more preferably it is -*O-CO-R_2 wherein

R_2 is C_1-C_8 alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, C_{3-7} cycloalkyl-C_{1-4} alkyl, aryl-C_{1-4} alkyl or heteroaryl-C_{1-4} alkyl.

Preferred mevinolins of the invention for use as LFA-1 antagonist are compounds of formula I

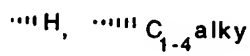


I

wherein

R_2 is as defined above,

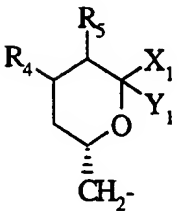
R_1 is



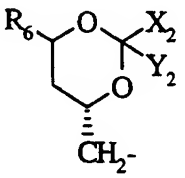
H, C_{1-4}alkyl or OR_a;

R_a is H; C_{1-6} alkyl; C_{1-6} alkyl substituted by OH or C_{1-4} alkoxy; C_{2-6} alkenyl; or aryl-C_{1-4} alkyl;

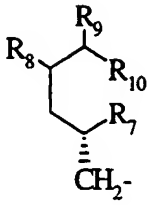
R_3 is a radical of formula (i), (ii), (iii) or (iv)



(i)

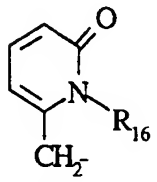


(ii)



(iii)

or



(iv)

wherein

X_1 and Y_1 are (H,H), (H,OH) or =O;

X_2 and Y_2 are =O or (R,R) wherein each R independently is H, C_{1-3} alkyl, substituted C_{1-3} alkyl or X_2 and Y_2 form together with the cabon atom to which they are bound a 4-, 5-, 6- or 7- membered carbo- or heterocyclic residue,

R_4 is OR_a wherein R_a is as defined above; or -O-COR_b wherein R_b is C_{1-8} alkyl optionally substituted by OH, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl or heteroaryl-C_{1-4} alkyl; or NR_cR_d wherein each of R_c and R_d, independently, is C_{1-6}alkyl or form together with the nitrogen to which they are bound a heterocyclic radical optionally comprising an oxygen or another nitrogen atom;

R_5 is H, C_{1-4} alkyl, C_{3-9} alkenyl, C_{3-9} alkynyl, aryl-C_{1-4} alkyl, or C_{3-7} cycloalkyl-C_{1-4} alkyl;

R_6 is -CHR_{11}-CO-$NR_{12}R_{13}$ wherein R_{11} has one of the significances as given for R_5 and each R_{12} and R_{13}, independently, is H, C_{1-4} alkyl, or substituted C_{1-4} alkyl;

R_7 is =O or (H,OH);

R_8 is OR_a; or NR_eR_f wherein each of R_e and R_f, independently, is H, C_{1-6}alkyl, C_{1-6}alkyl substituted by OH or C_{1-4}alkoxy, or a 5-membered heterocyclic residue;

or R_7 and R_8 together form a dioxy-C_{1-4}alkylene group or -O-CO-O-;

R_9 has one of the significances given for R_5;

R_{10} is $COOR_a$; CH_2OR_c wherein R_c is R_a or COR_b; or $CONR_{14}R_{15}$ or $CH_2NR_{14}R_{15}$ wherein each of R_{14} and R_{15} independently is C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, carbamoyl-methyl, (C_{1-4}alkyl)-carbamoyl-methyl or di(C_{1-4}alkyl)-carbamoyl-methyl, or one of R_{14} and R_{15} is hydrogen and the other is C_{1-6}alkyl, C_{1-6}alkyl substituted by OH and/or a group selected from carbamoyl, (C_{1-4}alkyl)-carbamoyl, di(C_{1-4}alkyl)-carbamoyl and heteroaryl-C_{1-4}alkyl, C_{1-6}alkoxy-carbonyl-methyl, adamantyl-methyl, C_{3-7}cycloalkyl-C_{1-4}alkyl, aryl-C_{1-4}alkyl wherein aryl may be substituted and C_{1-4}alkyl may be substituted by carbamoyl or C_{1-4}alkoxy-carbonyl, or heteroaryl-C_{1-4}alkyl wherein heteroaryl may be substituted by carbamoyl or C_{1-4}alkoxy-carbonyl and C_{1-4}alkyl may be substituted by carbamoyl, or R_{14} and R_{15} form together with the nitrogen to which they are attached a heterocyclic residue optionally comprising a further nitrogen atom and optionally substituted by C_{1-4}alkyl, (C_{1-4}alkoxy)-carbonyl, carbamoyl, dioxy-C_{1-4}alkylene, aryl-C_{1-4}alkyl or heteroaryl wherein heteroaryl may be substituted by C_{1-4}alkoxy-carbonyl;

R_{16} is H; C_{1-4}alkyl; aryl-C_{1-4}alkyl wherein aryl may be substituted by halogen, OH, amino optionally substituted, COOH, CF_3, C_{1-4} alkoxy or cyano; or C_{3-7}cycloalkyl-C_{1-4}aryl;

each of a---b and α---β independently, is either a single bond or a double bond,

in free form or in a pharmaceutically acceptable salt form.

Alkyl groups as R_a R_b, R_2, R_5, R_{11}, R_{12} or R_{13} or alkyl moieties may be branched or straight chain. When R, R_{12} or R_{13} is a substituted alkyl, the substituent is preferably located at the end of the alkyl chain and may be e.g. halogen, OH, C_{3-7} cycloalkyl or aryl. When R_e or R_f is substituted C_{1-6}alkyl, it is preferably substituted at the end of the alkyl chain.

Cycloalkyl groups or moieties are preferably cyclopentyl or cyclohexyl.

Aryl or aryl moiety is preferably phenyl and may be substituted, e.g. by halogen, OH, amino optionally substituted, COOH, CF_3, C_{1-4} alkoxy or cyano, preferably by 1,2 or 3 C_{1-4}alkoxy. Aryl-C_{1-4} alkyl is preferably phenyl-C_{1-4} alkyl, e.g. benzyl or phenethyl.

Heteroaryl is preferably derived from a 5- or 6- membered heterocycle optionally fused to a benzene ring, e.g. pyrrolyl, imidazolyl, furyl, thienyl, pyridyl, indolyl etc. When R_c and R_d form together with the nitrogen to which they are attached a heterocyclic radical, this may be a 5- or 6-membered ring, e.g. pyrrolidinyl, piperidyl, piperazinyl, 4-methyl-piperazinyl. When one of R_{14} or R_{15} is heteroaryl-C_{1-4}alkyl, the heteroaryl moiety may be a 5- or 6- membered, optionally fused to a benzene ring or a heterocyclic residue, e.g. furyl, morpholino, piperazinyl or indolyl. When R_{14} and R_{15} form together with the nitrogen to which they are attached a heterocyclic residue, this may be e.g. pyrrolidinyl, piperidino, piperazinyl.

When X_2 and Y_2 form a carbo- or heterocyclic residue, it may be e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, pyrrolidinyl, pyrrolidonyl.

The alkylene moiety in dioxy-C_{1-4}alkylene may be linear, e.g. $-CH_2-$, $-CH_2-CH_2-$, or branched, e.g. $=C(CH_3)_2$.

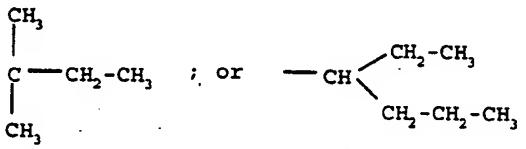
Compounds of formula I may exist in free form or in salt form, e.g. acid addition salts with e.g. organic or inorganic acids, for example, hydrochlorides, or salt forms obtainable when a COOH is present, as salts with bases e.g. alkali salts such as sodium or potassium, or substituted or unsubstituted ammonium salts.

It will be appreciated that in the residues of formulae (i), (ii) and (iii) the carbon atoms bearing R_4, R_5, R_6, R_7, and R_8 may be asymetric. Where in the molecule of formula I the stereochemistry is not indicated, it is to be understood that the present invention embraces all enantiomers and their mixtures. Similar considerations apply in relation to starting materials exhibiting asymetric carbon atoms as mentioned above.

In the compounds of formula I, the following significances are preferred:

1. R_1 is H or CH_3, preferably CH_3;

2. R_2 is C_{4-8}alkyl, preferably $-CH(CH_3)-CH_2-CH_3$; $-CH(CH_2-CH_2-CH_3)_2$-; $-CH(CH_2CH_3)_2$;



3. R_3 is a radical of formula (i);

4. R_3 is a radical of formula (iii);

5. R_3 is a radical of formula (iii) wherein R_7 is (H,OH);

6. R_3 is a radical of formula (iii) wherein R_7 is =O;

7. R_3 is a radical of formula (iii) wherein R_8 is OH;

8. R_3 is a radical of formula (iii) wherein R_7 and R_8 form together a dioxy-C_{1-4}alkylene group or -O-CO-O-;

9. R_3 is a radical of formula (iii) wherein R_8 is NR_eR_f;

10. R_3 is a radical of formula (iii) wherein R_8 is NHR_f wherein R_f is C_{1-6}alkyl optionally substituted by OH or C_{1-4}alkoxy;

11. R_3 is a radical of formula (iii) wherein R_9 is H, CH_3, benzyl or propargyl;

12. R_3 is a radical of formula (iii) wherein R_{10} is $CONR_{14}R_{15}$;

13. R_3 is a radical of formula (iii) wherein R_{10} is $CONHR_{15}$ wherein R_{15} is C_{1-4}alkyl optionally substituted by OH;

14. R_3 is a radical of formula (iii) wherein R_{10} is $CONHR_{15}$ wherein R_{15} is phenyl-C_{1-4}alkyl or heteroaryl-C_{1-4}alkyl wherein the phenyl, heteroaryl and C_{1-4}alkyl moieties may be substituted as indicated above. Preferably phenyl is substituted by 1, 2 or 3 C_{1-4}alkoxy, particularly OCH_3;

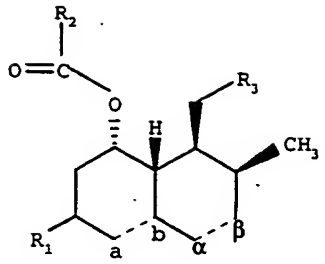
15. R_{15} is CH_2-phenyl or $CH(CO\text{-}OCH_3)$-phenyl wherein phenyl may be substituted by 1,2 or 3 C_{1-4}alkoxy, preferably OCH_3;

16. R_{15} is CH_2-furyl or $CH(CONH_2)\text{-}CH_2$-3-indolyl;

17. R_{10} is $-CONR_{14}R_{15}$ wherein R_{14} and R_{15} form together with the nitrogen to which they are attached an optionally substituted piperidinyl group, e.g. substituted by dioxy-C_{1-4}alkylene, preferably dioxy-ethylene;

18. R_3 is a radical of formula (iv).

Among the mevinolins of formula I, the compounds of formula II



II

wherein

R_1, R_2, R_3 and the doted lines a---b and α---β are as defined above,

provided that

1) R_2 is other than C_{1-5} alkyl or aryl-C_{1-4} alkyl when R_1 is H, CH_3 or C_2H_5 and R_3 is a radical of formula (i) wherein R_4 is OH or OCH_3, R_5 is H or C_{1-4} alkyl, and X_1 and Y_1 are = O, or

2) R_2 is other than C_{1-5} alkyl when R_3 is a radical of formula (iii) wherein R_9 is H and R_{10} is $COOR_a$,

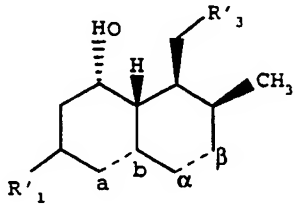
or salt thereof, are novel and form part of the present invention.

Particularly preferred compounds of formula II are those wherein

1. R_1 is H or CH_3, preferably CH_3
2. R_2 is C_{4-8}alkyl, preferably as disclosed above;
3. R_3 is a radical of formula (iii);
4. R_3 is a radical of formula (iii) wherein R_8 is NHR_f wherein R_f is C_{1-6}alkyl optionally substituted by OH or C_{1-4}alkoxy;
5. R_3 is a radical of formula (iii) wherein R_{10} is $CONHR_{15}$ wherein R_{15} is C_{1-4}alkyl optionally substituted by OH, preferably OH substituted C_{1-4}alkyl;
6. R_3 is a radical of formula (iii) wherein R_{10} is $CONHR_{15}$ wherein R_{15} is phenyl-C_{1-4}alkyl wherein the phenyl moiety may be substituted by 1, 2 or 3 C_{1-4}alkoxy, preferably OCH_3.

The present invention also includes a process for the production of the compounds of formula II, comprising

a) for the production of a compound of formula II wherein R_3 is a radical of formula (i) or (ii) reacting a compound of formula III



III

wherein a---b and α---β are as defined above, R'_1 has one of the significances given for R_1 except that the OH group as R_1 has to be in protected form and R'_3 is a radical of formula (i) or (ii)

with a compound of formula IV

$$R_2\,COOH \qquad IV$$

wherein R_2 is as defined above, or a functional derivative thereof, or

b) converting mevinolin or compactin into a compound of formula I;

and, where required, removing the protecting group, and recovering the compounds of formula II thus obtained in free form or in salt form.

Where OH groups are present in the starting products which are not to participate in the reaction, they may be protected, in accordance with known methods. OH protecting groups are known in the art, e.g. t.-butyl-dimethyl-silanyl.

Process step a) may be performed in accordance with known esterification methods. A functional derivative of a compound of formula IV includes e.g. an acid halogenide, ester or anhydride.

Process step b) may be a substitution in position 5 or a reduction of the pyranyl residue, e.g. as disclosed in Example 3. The R_2-CO-O- group of mevinolin may also be reduced to OH and then esterified to another R_2-CO-O- group. To produce compounds of formula II wherein R_3 is a residue of formula (iii) where R_{10} is $CONR_{14}R_{15}$, a compound of formula II wherein R_3 is a radical of formula (i) or (ii) e.g. mevinolin or compactin, may be submitted to ring opening, e.g. by reaction with a corresponding amine, e.g. alkylamine, HO-alkyl-amine, heterocyclic amine, or via the azide route. When R_7 is (H,OH), it may be oxidized to =O in accordance with known oxidation methods, e.g. with sulfur trioxide in form of a pyridine complex or according to a Swern oxidation. The preparation of compounds of formula II wherein R_7 and R_8 in the radical of formula (iii) form together a carbonate or dioxy-alkylene group, may be performed according to known methods, e.g. using preferably carbonyldiimidazole for the carbonate, or via ketal formation for the dioxy-alkylene group.

Process step b) may also be a cyclisation of a compound of formula II wherein R_3 is a radical of formula (iii) to produce a compound of formula II wherein R_3 is a radical of formula (i) or (iv). The cyclisation may advantageously be performed in the presence of a base e.g. Hunig's base and an activating agent, e.g. trifluoromethane sulfonic anhydride. The preparation of a compound of formula II wherein R_3 is a radical of formula (iv) may conveniently be performed using a compound of formula II wherein R_3 is a radical of formula (iii) wherein R_{10} is $CONHR_{15}$ and R_7 is oxidized to =O. Cyclisation may be carried out by acidic treatment, e.g. using trifluoroacetic acid.

Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art, as disclosed by Y. Chapleur, in "Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products", Springer Verlag, 1993, vol. 2, 829-93.

The present invention further provides:

8. A compound of formula II or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. in the treatment or prevention of disorders or diseases as indicated above.

9. A pharmaceutical composition comprising a compound of formula II, or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier therefor.

The following examples are illustrative of the invention.

Example 1: 2-ethyl-butyric acid 8-[2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a solution of 152 mg (0.350 mmol) of 4-(tert-butyl-dimethyl-silanyloxy)-6-[2-(8-hydroxy-2,6-dimethyl-1,2,6,7,8,8a-hexahydro-naphthalen-1-yl)-ethyl]-tetrahydro-pyran-2-one in 2 ml of pyridine are added 927 mg (4.39 mmol) of 2-ethyl-butyric acid anhydride and the mixture is stirred overnight at room temperature. The reaction is quenched with saturated aqueous sodium bicarbonate. The aqueous phase is separated and extracted twice with methyl-t-butyl ether. The organic phases are combined, washed with a 10% citric acid solution and dried over sodium sulfate. The crude product is dissolved in 5 ml of THF containing 75 mg (1.3 mmol) acetic acid and 0.3 g (1 mmol) of tetrabutyl ammonium fluoride trihydrate are added. After 20 hours at room temperature the reaction is quenched with saturated aqueous sodium bicarbonate. The phases are separated and the water phase is extracted twice with ethyl acetate. The organic phases are combined, washed with brine and dried over sodium sulfate. After evaporation of the solvent, the crude product is purified by silica gel chromatography (methyl-t-butyl ether) to afford the desired product which is recrystallized from diethyl ether/hexane.

m.p. 120-122° C (diethyl ether/hexane)

MS (ESI) 441 (M+Na), 419 (M+H)

Example 2: 2-methyl-butyric acid 8-[2-(5-benzyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a stirred, cooled (- 77° C) solution of 101 mg (1.00 mmol) of diisopropylamine in 5 ml of THF under argon are added 0.63 ml (1.0 mmol) of a 1.6 M butyllithium solution in hexane.

After 15 minutes, 202 mg (0.50 mmol) of mevinolin are added and the reaction mixture is kept at - 77° C for 30 minutes. Then 171 mg (1.0 mmol) benzyl bromide are added. After 2 hours the reaction is let come to room temperature and poured onto 0.1 N aqueous HCl. The phases are separated and the aqueous phase is extracted twice with ethyl acetate. The organic phases are combined, washed with brine and dried over sodium sulfate. The solvent is evaporated and the crude product is purified by silica gel chromatography (diethyl ether/hexane 2/1) to afford the desired product as a colorless oil.
MS (FAB) 495 (M+H), 393

Example 3: 2-methyl-butyric acid 8-[2-(4-hydroxy-tetrahydro-pyran-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a solution of 65 mg (0.15 mmol) of mevinolin in 5 ml of ethanol are added 22 mg (1.0 mmol) lithium borohydride and the resulting mixture is stirred overnight at room temperature. The reaction is quenched with 0.1 N aqueous HCl. The phases are separated and the aqueous phase is extracted twice with ethyl acetate. The organic phases are combined, washed with brine and dried over sodium sulfate. The solvent is evaporated and the crude product purified by silica gel chromatography (ethyl acetate) to afford 2-methyl-butyric acid 3,7-dimethyl-8-(3,5,7-trihydroxy-heptyl)-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester as an oil.
MS (ESI) 431 (M+Na), 409 (M+H)

To a cooled (- 77° C) solution of 73 mg (0.18 mmol) of 2-methyl-butyric acid 3,7-dimethyl-8-(3,5,7-trihydroxy-heptyl)-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 5 ml of methylene chloride is added 0.9 g (7 mmol) Hunig's base and 0.08 ml (0.5 mmol) triflic anhydride. After 30 minutes the reaction is quenched with saturated aqueous sodium bicarbonate. The phases are separated and the water phase is extracted twice with ethyl acetate. The organic phases are combined, washed with brine and dried over sodium sulfate. The solvent is evaporated and the crude product is purified by silica gel chromatography (diethyl ether/hexane 1/4) to afford the desired product as a colorless oil.
MS (FAB) 391 (M+H), 289

Example 4: 2-methyl-butyric acid 8-(6-benzylcarbamoyl-3,5-dihydroxy-hexyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthlen-1-yl ester

To a solution of 0.13 g (0.32 mmol) of mevinolin in 15 ml of THF are added 0.5 ml (5 mmol) benzylamine. The stirred reaction mixture is heated at reflux for 7 hours. After cooling to room temperature the reaction is diluted with 20 ml of methyl-t-butyl ether and washed successively with 0.1 N HCl and brine. The organic phase is then dried over sodium sulfate and the solvent evaporated. The crude product is purified by silica gel chromatography (ethyl acetate) to afford the desired product as an oil.
MS (ESI) 534 (M+Na), 512 (M+H)

Example 5: Preparation of the compound 33 in Table 3

A solution of 200 mg Mevinolin in 5 ml THF and 1.0 ml Hydrazine-Hydrat (25% in H_2O) is stirred at room temperature for 15 hours. After concentration, the reaction mixture is diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated. 2-Methyl-butyric acid 8-(6-hydrazinocarbonyl-3,5-dihydroxy-hexyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester cristallizes from Et_2O.

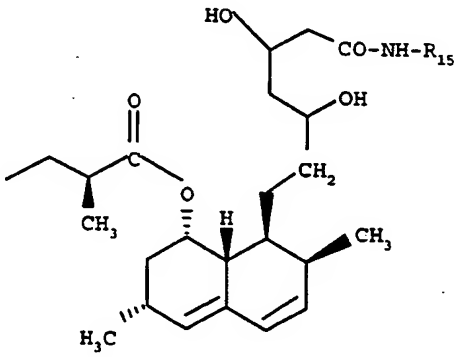
To a stirred, cooled solution (-15°C) of 86 mg of the above hydrazide are successively added 1.0 ml of 5N HCl in Et_2O and 0.36 ml of a 10% solution of tert.-butylnitrite in DMF. After 15 minutes stirring at -15°C, 0.15 ml NEt_3 and 0.06 ml 1,4-dioxa-8-azaspiro[4,5]decane are added. The reaction mixture is stirred 15 hours at 0°C then concentrated under reduced pressure, diluted with EtOAc, washed with 0.1N HCl, brine, sodium bicarbonate, brine, dried (Na_2SO_4) and concentrated. The product of Example 33 is obtained after cristallization with diisopropylether.
MS (ESI): 548 $MH^{\oplus}$

Example 6: 2-methyl-butyric acid 8-[3-hydroxy-5-(2-hydroxy-ethylamino)-6-(2-hydroxy-ethylcarbamoyl)-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a stirred solution of 4.0 g (10 mmol) mevinolin in 20 ml pyridine at room temperature are added 20 ml acetic acid anhydride. After 1 h the reaction mixture is concentrated *in-vacuo*. The residue is dissolved with 10 ml methyl-t-butyl ether and washed successively with water, 0.1 N HCl and brine. The organic phase is then dried over sodium sulfate and the solvent removed in vacuo. The crude product is purified by silica gel chromatography (methyl-t-butyl ether 1/3) to afford 2-methyl-butyric acid 3,7-dimethyl-8-[2-(6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester) as a white powder.

To a stirred solution of 1.2 g (3.0 mmol) (methyl-t-butyl ether 1/3) to afford 2-methyl-butyric acid 3,7-dimethyl-8-[2-(6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester) in 10 ml THF at room temperature are added 1.5 ml (25 mmol) ethanol amine. After 12 h the solvent is evaporated and the residue dissolved in 10 ml ethyl acetate. The solution is washed with 5 ml saturated aqueous sodium bicarbonate and 5 ml brine. The solution is then dried over sodium sulfate and the solvent evaporated to afford the title product as a hygroscopic foam.
MS (ESI) 515 (M+Li), 509 (M+H).

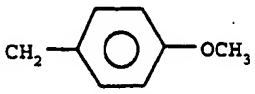
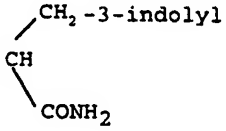
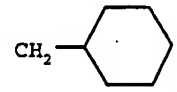
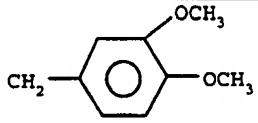
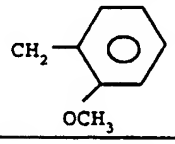
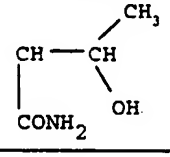
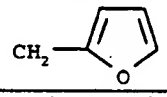
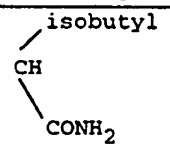
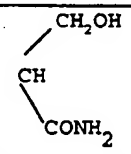
By following the procedures as disclosed above in the Examples, but using the appropriate starting materials, the compounds of formula X_1

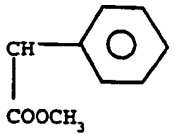


X_1

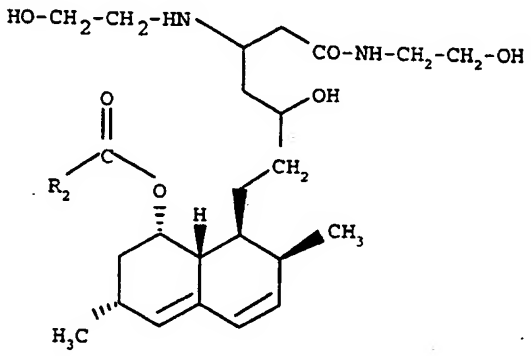
wherein R_{15} is as defined in Table 1 below, may be prepared.

Table 1

Ex	R_{15}	MS		
7		ESI	542	MH^+
8		ESI	606	MH^-
9	isobutyl	FAB	478	MH^+
10	CH_2-CO-O-t.butyl	FAB	536	MH^+
11		FAB	518	MH^+
12		FAB	572	MH^+
13	$C(CH_2\text{-}OH)_3$	ESI	524	MH^-
14	CH_2-CH_2-morpholino	ESI	535	MH^+
15		ESI	542	MH^+
16		ESI	521	MH^-
17		ESI	502	MH^+
18		FAB	535	MH^+
19		ESI	507	MH^-
20	CH_2-CO-$N(CH_3)_2$	FAB	507	MH^+

21		ESI	568	MH^-
22	$CH(CH_3)$-$CONH_2$	ESI	491	MH^-

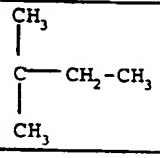
By following the procedures as disclosed above in the Examples, but using the appropriate starting materials, the compounds of formula X_2



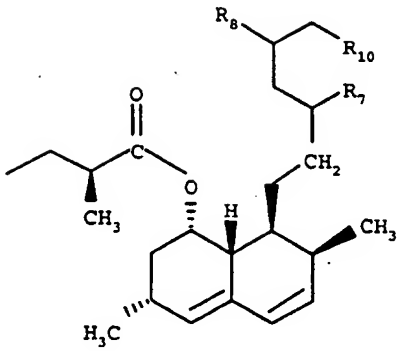
X_2

wherein R_2 is as defined in Table 2 below, may be prepared.

Table 2

Ex	R_2	MS		
23	$CH(CH_2$-CH_2-$CH_3)_2$	FAB	557	$M+Li^+$
24		FAB	529	$M+Li^+$

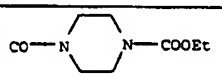
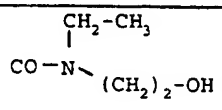
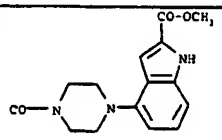
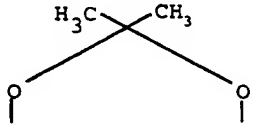
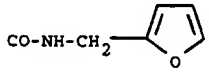
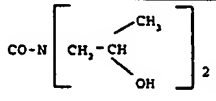
By following the procedures as disclosed above and below, but using the appropriate starting materials, the compounds of formula X_3

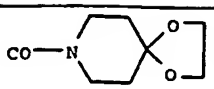
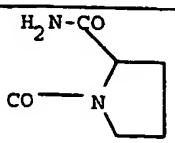
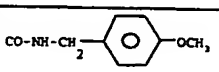
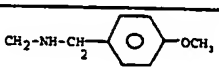
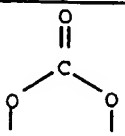
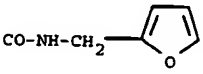
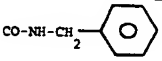
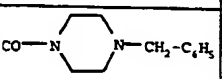
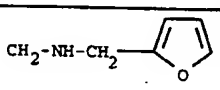
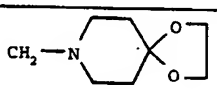
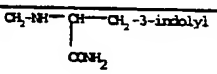
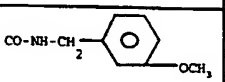


X_3

wherein R_7, R_8 and R_9 are as defined in Table 3 below, may be prepared.

Table 3

Ex	R_7	R_8	R_{10}	MS
25	OH	piperazinyl	$CO\text{-}OC_2H_5$	FAB 539 $M+Li^+$
26	OH	OH	$CO\text{-}N(CH_3)_2$	FAB 450 MH^+
27	OH	OH		ESI 563 MH^+
28	OH	OH		ESI 494 MH^+
29	OH	OH		ESI 562 MH^-
30				ESI 542 MH^+
31	OH	OH		ESI 538 MH^+
32	OH	OH	$CO\text{-}N(CH_3)\text{-}CH_2\text{-}CO\text{-}N(CH_3)_2$	ESI 521 MH^+

33	OH	OH		ESI 548 MH^+
34	OH	OH		ESI 519 MH^+
* 35	=O	OH		ESI 529 M^+HCOO^-
** 36	OH	OH		ESI 548 MH^+
*** 37				ESI 528 MH^+
38	=O	OH		FAB 516 $M+Li^+$
39	=O	OH	$CO\text{-}NHCH_3$	FAB 440 $M+Li^+$
40	OH	OH		FAB 581 MH^+
41	OH	OH		ESI 488 MH^+
42	OH	OH		ESI 534 MH^+
43	OH	OH		ESI 592 MH^-
44	OH	OH		ESI 540 MH^-

* Oxidation Example (Compound of Ex. 35)

A solution of 0.18 ml oxalyl chloride in 10 ml CH_2Cl_2 is slowly treated at -60°C with 0.33 ml DMSO. After 15 minutes stirring at -60°C a cold solution (-78°C) of 2-methyl-butyric acid 8-

[5-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-6-(4-methoxy-benzylcarbamoyl)-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 5 ml CH_2Cl_2 is added. After 2 hours at -60°C, 0.80 ml of NEt_3 is added and the temperature is slowly rised to room temperature. After 2 hours at room temperature the reaction is quenched with H_2O. The phases are separated and the organic phase dried and concentrated. The crude product is purified by silica gel chromatography (CH_2Cl_2/MeOH). The resulting compound is dissolved in THF and treated with AcOH and $Bu_4NF.3H_2O$. After 30 hours the reaction mixture is concentrated, diluted with AcOEt and washed with H_2O, sat. $NaHCO_3$, brine, then dried (Na_2SO_4) and concentrated. The crude product is purified by silica gel chromatography. Pure fractions are combined and evaporated to afford 2-methyl-butyric acid 8-[5-hydroxy-6-(4-methoxy-benzylcarbamoyl)-3-oxo-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester as foam.

** Reduction Example (Compound of Ex. 36)

To a solution of 2.0 g 2-methyl-butyric acid 8-{2-[4-(tert-butyl-dimethyl-silanyloxy)-6-oxo-tetrahydropyran-2-yl]-ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 12 ml abs. THF under argon are slowly added under stirring at -78°C 8.0 ml di-isobutyl aluminiumhydride (1 M) in THF. After 30 minutes stirring at -78°C, a mixture of 1.5 ml MeOH in 3 ml THF is slowly added. After 15 minutes, the reaction mixture is concentrated, diluted with EtOAc and washed with 10% citric acid, H_2O, sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated in vacuo. The lactol is obtained as a foam and stored at -20°C. 300 mg of the crude lactol in a mixture of 10 ml DMF and 1 ml AcOH under argon are treated with 74 mg $NaCNBH_3$ and 0.25 ml 4-methoxybenzylamine. After stirring at room temperature for 40 hours the reaction mixture is concentrated in vacuo, diluted with AcOEt and cold 1N HCl and stirred for 30 minutes. The organic phase is further washed with brine, sat. $NaHCO_3$, brine, dried and concentrated. The crude product is purified by silica gel chromatography (CH_2Cl_2/MeOH 95:5) to afford 2-methyl-butyric acid 8-[5-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-7-(4-methoxy-benzylamino)-heptyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester.

For deprotection the product is treated at room temperature with a mixture of 2 ml THF containing 20 µl AcOH and 77 mg tetrabutyl ammonium fluoride trihydrate. After stirring for

30 hours the reaction mixture is concentrated, diluted with AcOEt, washed with H_2O, sat. $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated. 2-Methyl-butyric acid 8-[3,5-dihydroxy-7-(4-methoxy-benzylamino)-heptyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester is obtained as a foam.

*** Conversion of Compound of Ex 17 into Compound of Ex 37

100 mg of compound of Ex 17 in 2 ml CH_2Cl_2 are treated with 73 mg DMAP, and 0.13 ml phosgen (2 M) in toluene. After stirring at room temperature overnight, the reaction mixture is quenched with sodium bicarbonate. The reaction mixture is then concentrated, diluted with Et_2O and successively washed with in HCl, H_2O, sat. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The desired product is cristallized from Et_2O/diisopropylether. (DMAP = dimethylamino-pyridine).

Example 45: 2-methyl-butyric acid 8-[2-(1-benzyl-6-oxo-1,6-dihydro-pyridin-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a stirred solution of 2.6 g (5.0 mmol) 2-methyl-butyric acid 8-{2-[4-(tert.-butyl-dimethyl-silanyloxy)-6-oxo-tetrahydro-pyran-2-yl]-ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 50 ml toluene at room temperature are added 2.0 ml (18 mmol) benzylamine and 1 mg of Amberlite IP 120. The reaction mixture is heated at reflux for 18 hours. After cooling to room temperature the mixture is filtered, washed with 10% aqueous citric acid and dried over sodium sulfate. The solvent is evaporated to afford 2-methyl-butyric acid 8-[6-benzylcarbamoyl-5-(.tert.-butyl-dimethyl-silanyloxy)-3-hydroxy-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester as an oil. MS (FAB) m/z 632 ($[M+Li]^+$)

To a stirred solution of 2.9 g (4.6 mmol) 2-methyl-butyric acid 8-[6-benzylcarbamoyl-5-(tert.-butyl-dimethyl-silanyloxy)-3-hydroxy-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester and 5.2 ml (37 mmol) triethyl amine in 22 ml DMSO is added a solution of 4.4 g (28 mmol) SO_3.pyridine complex in 22 ml DMSO. After 2 hours at room temperature the mixture is poured on ice and extracted twice with ethyl acetate. The

combined organic phases are dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel (hexane/ethyl acetate 9/1 to 7/3) to afford 2-methyl-butyric acid 8-[6-benzylcarbamoyl-5-(tert.-butyl-dimethyl-silanyloxy)-3-oxo-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester as an oil. MS (FAB) m/z 630 ($[M+Li]^+$)

To a stirred solution of 200 mg (0.32 mmol) 2-methyl-butyric acid 8-[6-benzylcarbamoyl-5-(tert.-butyl-dimethyl-silanyloxy)-3-oxo-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 5 ml methylene chloride are added 0.3 g (2.6 mmol) trifluoroacetic acid. After 2 hours at room temperature the reaction mixture is quenched with saturated aqeous sodium bicarbonate. The aqueous phase is separated and extracted twice with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is evaporated. The residue is chromatographed over silica gel (hexane/ ethyl acetate 7/3 to 2/3) affording the title compound as a white powder foam. MS (FAB) m/z 480 ($[M+Li]^+$)

Example 46: 2-methyl-butyric acid 3,7-dimethyl-8-[2-(6-oxo-1,6-dihydro-pyridin-2-yl)-ethyl]-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a stirred solution of 1.0 g (1.9 mmol) 2-methyl-butyric acid 8-[5-(tert.-butyl-dimethyl-silanyloxy)-6-carbamoyl-3-oxo-hexyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 25 ml methylene chloride are added 0.7 g (6.5 mmol) trifluoroacetic acid. After 2 hours at room temperature the reaction mixture is quenched with saturated aqueous sodium bicarbonate. The aqueous phase is separated and extracted twice with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is evaporated. The residue is chromatographed over silica gel (hexane/acetone 1/1) to afford the title compound as a white foam. MS (FAB) m/z 384 ($[M+H]^+$)

Example 47: 2-methyl-butyric acid 3,7-dimethyl-8-[2-(1-methyl-6-oxo-1,6-dihydro-pyridin-2-yl)-ethyl]-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester

To a stirred solution of 77 mg (0.2 mmol) 2-methyl-butyric acid 3,7-dimethyl-8-[2-(6-oxo-1,6-dihydro-pyridin-2-yl)-ethyl]-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester in 5 ml DMF are added 0.1 g (0.8 mmol) potassium carbonate and 0.1 g (0.8 mmol) methyl iodide. After 2 hours at room temperature the mixture is poured on water. The aqueous phase is separated and extracted twice with ethyl acetate. The combined organic phases are dried over sodium sulfate and the solvent is evaporated in vacuo. The residue is chromatographed over silica gel eluting with hexane/acetone 1/1 to afford the title compound as white powder.
MS (FAB) m/z 404 ($[M+Li]^+$)

Example 48: 2-ethyl-butyric acid 8-[2-(1-benzyl-6-oxo-1,6-dihydro-pyridin-2-yl)-ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro-naphthalen-1-yl ester
MS(ESI): 487 M^+

Compounds of e.g. Examples 6, 15 and 33 are preferred for the prevention or treatment of disorders or diseases mediated by LFA-1/ICAM-1 or ICAM-3 interactions, e.g. ischemia/reperfusion injury, chronic graft rejection. For example, in the Jurkat Cell Assay disclosed hereinbefore they have an IC_{50} of 4, 2.2. and 1.2 μM, respectively. In the murine thioglycollate induced peritonitis model the compounds of e.g. Ex. 6 and 33 fully inhibit the neutrophil migration when administered s.c. at a dose of 1 and 0.1 mg/kg, respectively.
It is therefore indicated that for the treatment or prevention of these disorders or diseases, the compounds may be administered to humans at a daily dosage from 5 to 750 mg.

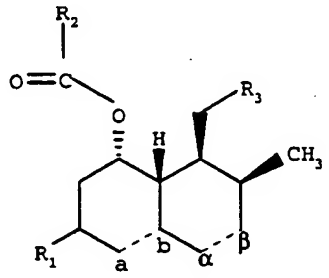
CLAIMS

1. A compound for use in the treatment and/or prevention of autoimmune diseases, acute or chronic inflammatory diseases, ischemia/reperfusion injury, acute or chronic rejection of organ or tissue allo- or xenografts or infection diseases by virtue of its LFA-1 inhibitory activity.

2. A compound which binds in whole or in part to the south pole pocket of LFA-1 I-domain defined by the amino acids Val 130, Leu 132, Phe 134, Phe 153, Val 157, Leu 161, Tyr 166, Thr 231, Val 233, Ile 235, Ile 255, Tyr 257, Ile 259, Lys 287, Leu 298, Glu 301, Leu 302, Lys 305,
in free form or in pharmaceutically acceptable salt form,
for use as a LFA-1 antagonist.

3. A compound according to claim 1 or 2 which is a mevinolin.

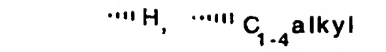
4. A compound according to claim 1 or 2, wherein the compound is a mevinolin of formula I



I

wherein

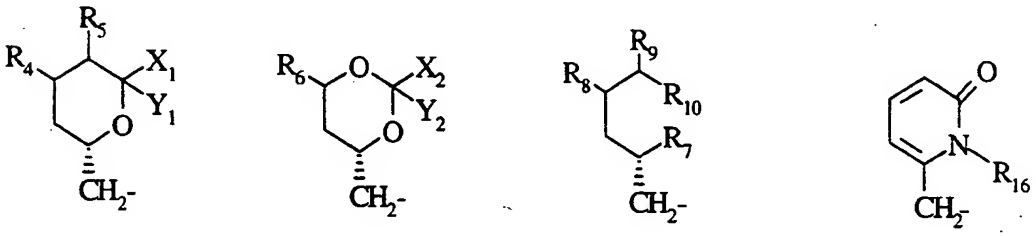
R_1 is



R_a is H; C_{1-6} alkyl; C_{1-6} alkyl substituted by OH or C_{1-4} alkoxy; C_{2-6} alkenyl; or aryl-C_{1-4} alkyl;

R_2 is C_{1-8}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl, C_{3-7}cycloalkyl-C_{1-4}alkyl, aryl-C_{1-4}alkyl or heteroaryl-C_{1-4}alkyl;

R_3 is a radical of formula (i), (ii), (iii) or (iv)



(i) (ii) (iii) or (iv)

wherein X_1 and Y_1 are (H,H), (H,OH) or =O;

X_2 and Y_2 are =O or (R,R) wherein each R independently is H, C_{1-3} alkyl, substituted C_{1-3} alkyl or X_2 and Y_2 form together with the cabon atom to which they are bound a 4-, 5-, 6- or 7- membered carbo- or heterocyclic residue,

R_4 is OR_a wherein R_a is as defined above; or -O-COR_b wherein R_b is C_{1-8} alkyl optionally substituted by OH, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl or heteroaryl-C_{1-4} alkyl; or NR_cR_d wherein each of R_c and R_d, independently, is C_{1-6}alkyl or form together with the nitrogen to which they are bound a heterocyclic radical optionally comprising an oxygen or another nitrogen atom;

R_5 is H, C_{1-4} alkyl, C_{3-9} alkenyl, C_{3-9} alkynyl, aryl-C_{1-4} alkyl, or C_{3-7} cycloalkyl-C_{1-4} alkyl;

R_6 is $-CHR_{11}-CO-NR_{12}R_{13}$ wherein R_{11} has one of the significances as given for R_5 and each R_{12} and R_{13}, independently, is H, C_{1-4} alkyl, or substituted C_{1-4} alkyl;

R_7 is =O or (H,OH);

R_8 is OR_a; or NR_eR_f wherein each of R_e and R_f, independently, is H, C_{1-6}alkyl, C_{1-6}alkyl substituted by OH or C_{1-4}alkoxy, or a 5-membered heterocyclic residue;

or R_7 and R_8 together form a dioxy-C_{1-4}alkylene group or -O-CO-O-;

R_9 has one of the significances given for R_5;

R_{10} is $COOR_a$; CH_2OR_c wherein R_c is R_a or COR_b; or $CONR_{14}R_{15}$ or $CH_2NR_{14}R_{15}$ wherein each of R_{14} and R_{15} independently is C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, carbamoyl-methyl, (C_{1-4}alkyl)-carbamoyl-methyl or di(C_{1-4}alkyl)-carbamoyl-methyl, or one of R_{14} and R_{15} is hydrogen and the other is C_{1-6}alkyl, C_{1-6}alkyl substituted by OH and/or a group selected from carbamoyl, (C_{1-4}alkyl)-carbamoyl, di(C_{1-4}alkyl)-carbamoyl and heteroaryl-C_{1-4}alkyl, C_{1-6}alkoxy-carbonyl-methyl, adamantyl-methyl, C_{3-7}cycloalkyl-C_{1-4}alkyl, aryl-C_{1-4}alkyl wherein aryl may be substituted and C_{1-4}alkyl may be substituted by carbamoyl or C_{1-4}alkoxy-carbonyl, or heteroaryl-C_{1-4}alkyl wherein heteroaryl may be substituted by carbamoyl or C_{1-4}alkoxy-carbonyl and C_{1-4}alkyl may be substituted by carbamoyl, or R_{14} and R_{15} form together with the nitrogen to which they are attached a heterocyclic residue optionally comprising a further nitrogen atom and optionally substituted by C_{1-4}alkyl, (C_{1-4}alkoxy)-carbonyl, carbamoyl, dioxy-C_{1-4}alkylene, aryl-C_{1-4}alkyl or heteroaryl wherein heteroaryl may be substituted by C_{1-4}alkoxy-carbonyl;

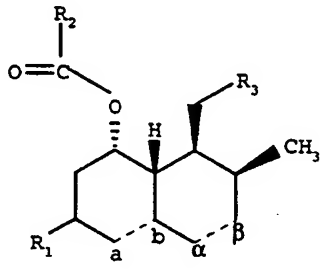
R_{16} is H; C_{1-4}alkyl; aryl-C_{1-4}alkyl wherein aryl may be substituted by halogen, OH, amino optionally substituted, COOH, CF_3, C_{1-4} alkoxy or cyano; or C_{3-7}cycloalkyl-C_{1-4}aryl;

each of a---b and α---β independently, is either a single bond or a double bond,

in free form or in a pharmaceutically acceptable salt form.

5. A compound according to claim 4, wherein R_1 is H or CH_3; R_2 is C_{4-8}alkyl; and R_3 is a radical of formula (i), (iii) or (iv) as defined in claim 4.

6. A compound of formula II



II

wherein

R_1, R_2, R_3 and the doted lines a---b and α---β are as defined in claim 4,

provided that

1) R_2 is other than C_{1-5} alkyl or aryl-C_{1-4} alkyl when R_1 is H, CH_3 or C_2H_5 and R_3 is a radical of formula (i) wherein R_4 is OH or OCH_3, R_5 is H or C_{1-4} alkyl, and X_1 and Y_1 are = O, or

2) R_2 is other than C_{1-5} alkyl when R_3 is a radical of formula (iii) wherein R_9 is H and R_{10} is $COOR_a$,

in free form or in salt form.

7. A compound according to claim 6, wherein R_1 is H or CH_3, R_2 is C_{4-8}alkyl and R_3 is a radical of formula (iii) wherein R_9 is other than H and R_{10} is other than $COOR_a$.

8. A pharmaceutical composition comprising a compound of formula II, in free form or in pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

9. A pharmaceutical composition for use as LFA-1 antagonist, comprising a compound which binds in whole or in part to the south pole pocket of LFA-1 I-domain defined by the amino acids Val 130, Leu 132, Phe 134, Phe 153, Val 157, Leu 161, Tyr 166, Thr 231, Val 233, Ile 235, Ile 255, Tyr 257, Ile 259, Lys 287, Leu 298, Glu 301, Leu 302, Lys 305,
in free form or in pharmaceutically acceptable salt form,
in association with a pharmaceutically acceptable diluent or carrier therefor.

10. A method for preventing or treating disorders or diseases mediated by LFA-1/ICAM-1 interactions, which method comprises administering to said subject an effective amount of a compound which which binds in whole or in part to the south pole pocket of LFA-1 I-domain defined by the amino acids Val 130, Leu 132, Phe 134, Phe 153, Val 157, Leu 161, Tyr 166, Thr 231, Val 233, Ile 235, Ile 255, Tyr 257, Ile 259, Lys 287, Leu 298, Glu 301, Leu 302, Lys 305,
in free form or in pharmaceutically acceptable salt form

11. A method for producing a chemical entity or ligand which associates with the LFA-1 I-domain south pole pocket comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and the south pole pocket; and

b. analyzing the results of said fitting operation to quantify the association between the chemical entity and the south pole pocket.

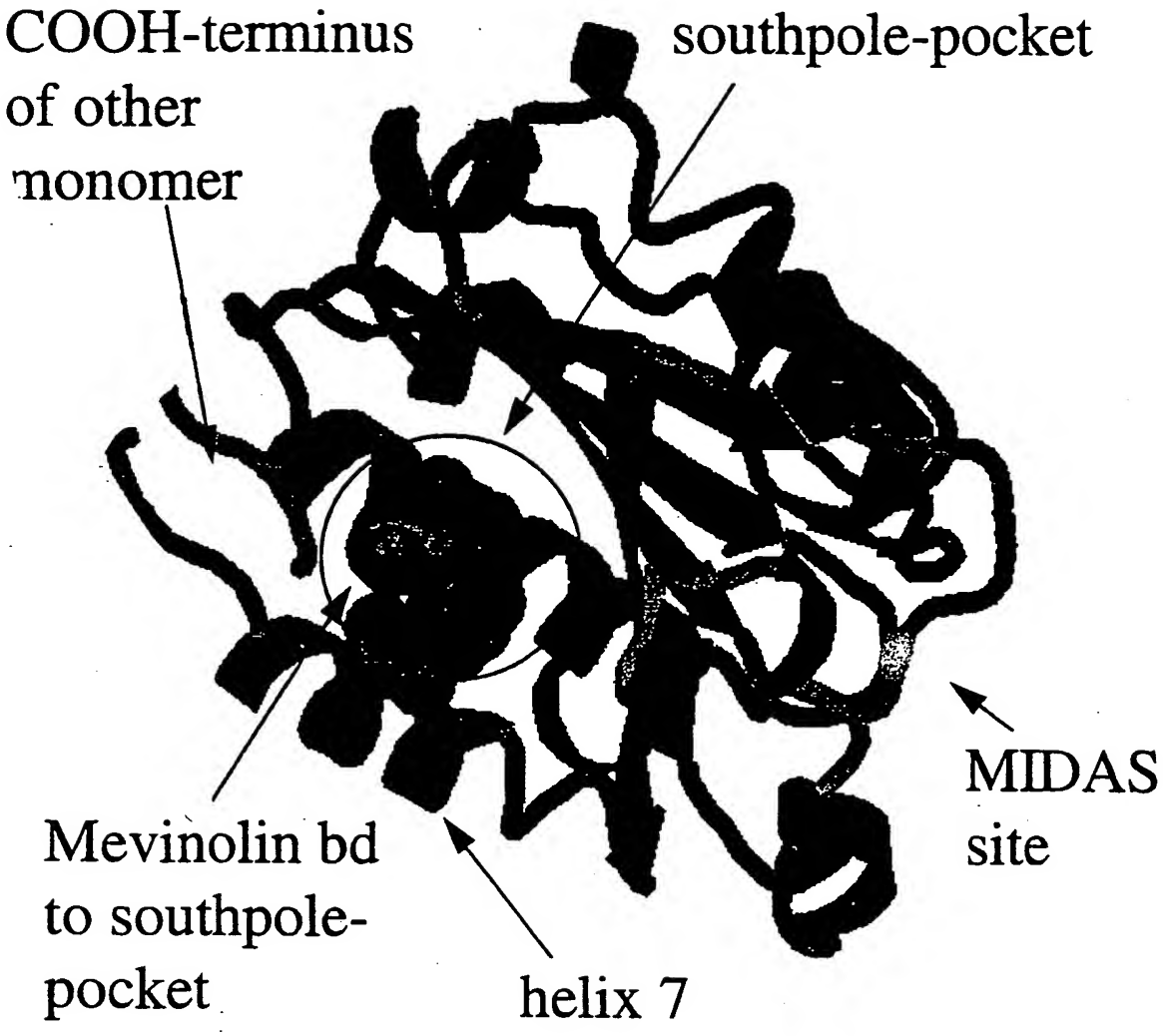
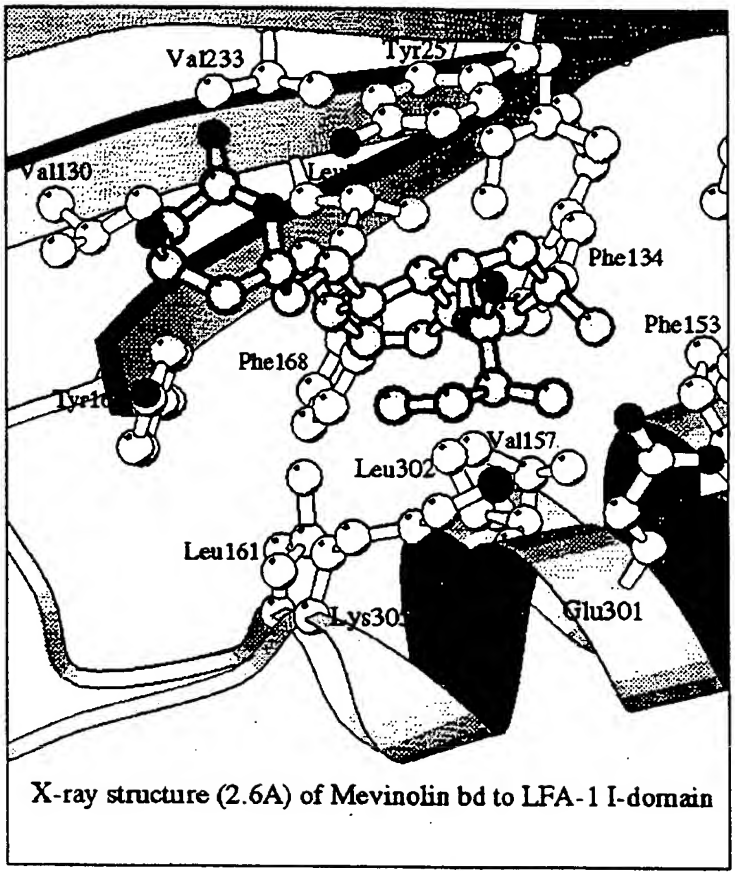

COOH-terminus of other monomer
southpole-pocket
MIDAS site
Mevinolin bd to southpole-pocket
helix 7

FIG. 1



X-ray structure (2.6A) of Mevinolin bd to LFA-1 I-domain

FIG. 2

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/05415

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/365 A61K31/22 A61K31/19 A61K31/44 C07D309/10
C07D309/30 C07D319/06 C07D213/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 072 002 A (THE GOVERNORS OF THE UNIVERSITY OF ALBERTA) 10 December 1991 see abstract see column 11 - column 13, line 27	1-6,8,9
X	US 4 611 081 A (MERCK & CO., INC.) 9 September 1986 see abstract see column 1, line 19 - column 4, line 8	1-6,8,9
X	US 4 665 091 A (MERCK & CO., INC.) 12 May 1987 see abstract see column 1, line 21 - column 2, line 2	1-6,8,9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 1999	03/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 678 806 A (MERCK & CO., INC.) 7 July 1987 see abstract see column 2, line 55 - column 4, line 11	1-9
X	US 5 116 870 A (MERCK & CO., INC.) 26 May 1992 see abstract see column 3, line 46 - column 10, line 58	1-9
X	US 4 876 366 A (MERCK &CO., INC.) 24 October 1989 see abstract see column 3, line 29 - column 6, line 38 see table 1 see tables 3,4	1-9
X	US 5 075 327 A (HOFFMANN-LA ROCHE INC.) 24 December 1991 see abstract see column 1, line 43 - column 5, line 7 see column 12, line 26 - line 54 see column 15, line 41 - column 16, line 30	1-6,8-10
X	US 5 620 876 A (E.R.SQUIBB & SONS, INC.) 15 April 1997 see column 1, line 18 - column 6, line 64	1-6,8,9
X	EP 0 033 537 A (MERCK & CO., INC.) 12 August 1981 see page 4, line 10 - line 31 see claims 1-8,11	1-6,8,9
X	EP 0 605 230 A (SANKYO CO. LTD.) 6 July 1994 see page 4, line 1 - page 26, line 14 see page 145, line 25 - page 146, line 30 see claims 1-21,31,32	1-6,8,9
X	EP 0 245 003 A (MERCK & CO., INC.) 11 November 1987 see claims 1-10	1-6,8,9
P,X	P. DI NAPOLI, A.BARSOTTI: "DOES 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR THERAPY EXERT A DIRECT ANTI-ISCHEMIC EFFECT?" CIRCULATION, vol. 97, no. 9, 10 March 1998, page 937 XP002090499 USA see abstract	1-10

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/05415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	K.WENKE ET AL.: "SIMVASTATIN REDUCES GRAFT VESSEL DISEASE AND MORTALITY AFTER HEART TRANSPLANTATION" CIRCULATION, vol. 96, no. 5, 2 September 1997, pages 1398-1402, XP002090500 USA see abstract see page 1401, right-hand column, line 1 - page 1402, left-hand column	1-10
X	SATORU NIWA ET AL.: "INHIBITORY EFFECT OF FLUVASTATIN, AN HMG-COA REDUCTASE INHIBITOR, ON THE EXPRESSION OF ADHESION MOLECULES ON HUMAN MONOCYTE CELL LINE" INT. J. IMMUNOPHARMACOL., vol. 18, no. 11, November 1996, pages 669-675, XP002090501 UK see the whole document	1-10
X	REICHART B. ET AL.: "WHAT IS THE ROLE OF LIPID LOWERING THERAPY IN HEART-ALLOGRAFT FAILURE" KIDNEY INT. SUPPL., vol. 48, no. SUPPL.52, December 1995, pages 52-55, XP002090502 USA see the whole document	1-10
X	GUO-ZHONG CHEN ET AL.: "ANTISCHISTOSOMAL ACTION OF MEVINOLIN: EVIDENCE THAT 3-HYDROXY-METHYLGLUTARYL-COENZYME A REDUCTASE ACTIVITY IN SCHISTOSOMA MANSONI IS VITAL FOR PARASITE SURVIVAL" NAUNYN SCHMIEDEBERGS ARCH PHARMACOL, vol. 342, no. 4, October 1990, pages 477-482, XP002090503 GERMANY see abstract see page 480, right-hand column, paragraph 2 - page 481, right-hand column, last paragraph	1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 98/05415

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5072002 A	10-12-1991	NONE	
US 4611081 A	09-09-1986	CA 1319700 A	29-06-1993
		EP 0207456 A	07-01-1987
		JP 62010044 A	19-01-1987
		US RE33033 E	22-08-1989
US 4665091 A	12-05-1987	NONE	
US 4678806 A	07-07-1987	CA 1302425 A	02-06-1992
		DE 3782702 A	24-12-1992
		EP 0259086 A	09-03-1988
		JP 63072660 A	02-04-1988
US 5116870 A	26-05-1992	US 4940727 A	10-07-1990
		AU 7455987 A	24-12-1987
		DK 317287 A	24-12-1987
		EP 0251625 A	07-01-1988
		JP 2582785 B	19-02-1997
		JP 63072652 A	02-04-1990
		ZA 8704487 A	23-12-1987
US 4876366 A	24-10-1989	CA 1310320 A	17-11-1992
		EP 0245990 A	19-11-1987
		JP 62277377 A	02-12-1987
		US 4937263 A	26-06-1990
US 5075327 A	24-12-1991	NONE	
US 5620876 A	15-04-1997	NONE	
EP 0033537 A	12-08-1981	AT 13534 T	15-06-1985
		DK 45981 A	05-08-1981
		GR 73077 A	31-01-1984
		IE 51477 B	07-01-1987
		JP 1036471 B	31-07-1989
		JP 1553298 C	04-04-1990
		JP 56122374 A	25-09-1981
		PT 72394 B	06-09-1982
		US 4351844 A	28-09-1982
EP 0605230 A	06-07-1994	AT 157346 T	15-09-1997
		AU 670468 B	18-07-1996
		AU 5269993 A	07-07-1994
		CA 2112442 A	29-06-1994
		CN 1094707 A,B	09-11-1994
		CZ 9302900 A	17-08-1994
		DE 69313427 D	02-10-1997
		DE 69313427 T	26-03-1998
		DK 605230 T	20-04-1998
		ES 2108238 T	16-12-1997
		FI 935895 A	19-10-1994
		GR 3025412 T	27-02-1998
		HU 65593 A	28-07-1994
		IL 108194 A	22-02-1998
		JP 6247894 A	06-09-1994
		MX 9400060 A	29-07-1994
		NO 934852 A	29-06-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/EP 98/05415

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0605230 A		NZ 250609 A	26-07-1995
		US 5451688 A	19-09-1995
		US 5827855 A	27-10-1998
		ZA 9309741 A	15-08-1994
EP 0245003 A	11-11-1987	US 4661483 A	28-04-1987
		US 4771071 A	13-09-1988
		CA 1310321 A	17-11-1992
		JP 62294641 A	22-12-1987
		US 4864038 A	05-09-1989
		US 4937264 A	26-06-1990
		US 4916162 A	10-04-1990